

## EDITORIAL COMMENT

# Single-Lead Ventricular Pacing Is No Longer an Option for Sick Sinus Syndrome\*

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In this issue of the *Journal*, Link et al. (1) report a study on the occurrence of pacemaker syndrome in the Mode Selection (MOST) trial. The MOST trial is the largest randomized trial of pacing mode selection in patients with sick sinus syndrome (SSS), including a total of 2,010 patients who all received rate-adaptive atrioventricular synchronous dual-chamber pacing (DDDR) pacemakers and were randomly assigned to dual-chamber or rate-adaptive inhibited single-lead ventricular (VVIR) pacing mode (N = 996) (2). The present study aimed to evaluate the incidence, predictors, and treatment of pacemaker syndrome in the 996 patients treated with VVIR pacing.

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Pacemaker syndrome occurred in 18.3% of the patients treated with VVIR pacing. The strongest predictor of pacemaker syndrome was a higher percentage of paced beats, and all significant predictors of pacemaker syndrome were parameters promoting or strongly associated with a higher percentage of ventricular paced beats. Pacemaker syndrome caused a marked decrease in quality of life, which improved significantly after reprogramming to DDDR pacing mode. Therefore, the present study adds a strong argument to always select an atrial based pacing mode for patients with SSS.

## DEFINING PACEMAKER SYNDROME

The definition of pacemaker syndrome has been variable, including several subjective symptoms as well as various objective findings (3,4). In the study by Link et al. (1), pacemaker syndrome was clearly defined as either “new or worsened dyspnea, orthopnea, elevated jugular pressure, rales, and edema with ventriculoatrial conduction during ventricular pacing” or “symptoms of dizziness, weakness, presyncope, or syncope and a >20 mm Hg reduction of systolic blood pressure when the patient was ventricular paced as compared with atrial pacing or sinus rhythm.” Both definitions include serious symptoms that had to occur

together with objective findings indicating an adverse hemodynamic effect of VVIR pacing. It is likely that the use of such strict definitions of pacemaker syndrome is associated with a more correct estimate of this syndrome.

## INCIDENCE OF PACEMAKER SYNDROME

Almost one-fifth of the patients treated with VVIR pacing developed pacemaker syndrome in the MOST trial (1). This incidence is similar to the 26% found in the Pacemaker Selection in the Elderly trial (5,6). In contrast, in the trial of inhibited single-lead ventricular pacing (VVI) versus inhibited single-lead atrial pacing (AAI), only 2% of patients had pacemaker syndrome that required a change in pacing mode (7), and in the large Canadian Trial Of Physiological Pacing (CTOPP), only 2.7% underwent pacing mode change because of pacemaker syndrome (8). In the two latter trials, hardware randomization was used, and the change in pacing mode to atrial-based pacing required a reoperation with implantation of an atrial lead and a new pacemaker. Therefore, it is likely that the threshold for diagnosing pacemaker syndrome was higher in these trials. A new operation not only results in an additional hospitalization and costs but also is associated with a risk of infection and other complications in each individual case.

Is 20% the correct incidence of pacemaker syndrome within the first years after pacemaker implantation in patients with SSS treated with VVIR pacing? In the study by Link et al. (1), the pacemaker programming followed usual recommendations in elderly patients with SSS, and in case of pacemaker syndrome, reprogramming of the pacemaker to reduce ventricular pacing was attempted before a change in pacing mode was performed. However, the investigators were not blinded with respect to the assigned pacing mode, and therefore an overreporting of pacemaker syndrome cannot totally be discounted. Furthermore, a placebo effect may have contributed to the improved quality of life after programming to atrial based pacing. However, the finding of a 20% incidence probably represents the best estimate of pacemaker syndrome in patients with SSS treated with VVIR pacing.

## PACING MODE IN PATIENTS WITH SSS

Two large randomized trials have tested VVIR pacing versus dual-chamber pacing in patients with SSS, the MOST trial (2) and the CTOPP trial (in which 42% of the 2,568 patients had SSS) (8). In both these trials, the incidences of the secondary end point “atrial fibrillation” (AF) were significantly less in the groups assigned dual-chamber pacing than in the VVIR groups. On the basis of these findings and because of the high—and not reliably predictable—incidence of pacemaker syndrome (1), VVIR pacing should no longer be used as the primary pacing mode in patients with SSS; DDDR pacing is a better choice. However, in both the MOST trial and the CTOPP trial, no

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significant differences were observed in the other end points, that is, mortality, cardiovascular deaths, heart failure (HF), or thromboembolism, between VVIR and DDDR pacing (2,8). In contrast, in the first randomized trial on pacing mode selection in SSS, single-lead atrial pacing was found to reduce not only AF but also total and cardiovascular mortality, HF, and thromboembolism as compared with VVI pacing (7,9). Recently, the first randomized comparison of rate-adaptive inhibited single-lead atrial pacing (AAIR) and DDDR pacing was published (10). In the AAIR group, no significant change was observed in left chamber diameters or left ventricular fractional shortening, whereas in the DDDR groups, left atrial diameter increased significantly and left ventricular fractional shortening decreased in those patients who were paced most. These findings document a detrimental effect of long-term single-site right ventricular pacing, so-called ventricular desynchronization. Right ventricular pacing induces an abnormal ventricular activation and contraction, which in turn leads to a reduced ventricular function and left atrial dilatation. Atrial fibrillation was significantly more common in the DDDR groups than in the AAIR group, indicating that ventricular desynchronization also promotes AF. The results of the AAIR versus DDDR trial are in accordance with the recent analysis from the MOST trial (11) and the results of the Dual Chamber and VVI Implantable Defibrillator trial (12). In both these trials, higher percentages of ventricular pacing were associated with excess HF, and in the MOST trial, also with excess AF (11). Ventricular desynchronization may also explain the relative modest differences in outcomes found in the large randomized comparisons of DDDR and VVIR pacing (CTOPP and MOST trials); the benefit of preserving atrioventricular synchrony was probably at least partly outweighed by the detrimental effects of ventricular desynchronization during DDDR pacing.

At present time, we consider AAIR pacing as the optimal pacing mode in patients with SSS not accompanied by atrioventricular (AV) block, bundle branch block, or carotid sinus syndrome. However, AAIR pacing does not protect the patients against high-degree AV block, which has been found to develop in 0.6% to 1.7% of the patients per year (13,14). Therefore, a larger randomized comparison between AAIR and DDDR pacing is necessary to definitively answer which pacing mode should be chosen for these patients. The ongoing Danish Multicenter Randomized Study on AAI or DDD Pacing in Sick Sinus Syndrome trial is expected to answer this question (15).

## FUTURE STUDIES

Fewer than 20% of the patients referred for primary pacemaker implantations are suitable for AAIR pacing (10), and the large majority of pacemaker patients have to be protected against or treated for AV block. If it was technically possible to confer this protection against AV block without

exposing the patients for the potential harmful effects of ventricular desynchronization, such a solution would be the best also for patients who today are treated with an AAIR pacemaker.

For patients without manifest AV block, new pacemaker algorithms should be developed to reduce ventricular pacing to a minimum and still protect the patients against AV block. Different AV hysteresis algorithms have already been implemented in newer pacemaker types; however, their performance in reducing ventricular pacing have only been studied sparsely and have not been impressive (16,17). To reduce ventricular stimulation to a minimum, it is necessary to leave the fundamental principle in dual-chamber pacing, that every atrial event must always be followed by a ventricular event—sensed or paced. This would allow a real mode-shift between AAIR and DDDR pacing modes (18).

For patients who need ventricular pacing most of the time, alternative strategies of pacing the ventricle(s) should be studied. Theoretically, selection of other ventricular pacing sites as well as multiple ventricular pacing sites might cause less ventricular desynchronization and thereby a better patient outcome.

In both cases, such trials on pacing mode selection should be powered to study not only the achieved percentages of ventricular paced beats, but also what is important for the patients: the clinical outcome—HF, AF, and mortality. Based on our present knowledge, VVIR pacing should no longer be considered an option for patients with SSS.

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## REFERENCES

1. Link MS, Hellkamp AS, Estes III NAM, et al., for the MOST Study Investigators. High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular-based pacing in the Mode Selection Trial (MOST). *J Am Coll Cardiol* 2004;43:2066–71.
2. Lamas GA, Lee KL, Sweeney MO, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;346:1854–62.
3. Ausubel K, Furman S. The pacemaker syndrome. *Ann Intern Med* 1985;103:420–9.
4. Ellenbogen KA, Gilligan DM, Wood MA, Morillo C, Barold SS. The pacemaker syndrome—a matter of definition. *Am J Cardiol* 1997;79:1226–9.
5. Lamas GA, Orav J, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. *N Engl J Med* 1998;338:1097–104.
6. Ellenbogen KA, Stambler BS, Orav EJ, et al. Clinical characteristics of patients intolerant to VVIR pacing. *Am J Cardiol* 2000;86:59–63.
7. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick sinus syndrome. *Lancet* 1997;350:1210–6.
8. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000;342:1385–91.
9. Nielsen JC, Andersen HR, Thomsen PE, et al. Heart failure and echocardiographic changes during long-term follow-up of patients

- with sick sinus syndrome randomized to single chamber atrial or ventricular pacing. *Circulation* 1998;97:987-95.
10. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. *J Am Coll Cardiol* 2003;42: 614-23.
  11. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003; 107:2932-7.
  12. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115-23.
  13. Kristensen L, Nielsen JC, Pedersen AK, Mortensen PT, Andersen HR. AV block and changes in pacing mode during long-term follow-up of 399 consecutive patients with sick sinus syndrome treated with an AAI/AAIR pacemaker. *Pacing Clin Electrophysiol* 2001;24: 358-65.
  14. Andersen HR, Nielsen JC, Thomsen PE, et al. Atrioventricular conduction during long-term follow-up of patients with sick sinus syndrome. *Circulation* 1998;98:1315-21.
  15. Andersen HR, Nielsen JC. Pacing in sick sinus syndrome—need for a prospective, randomized trial comparing atrial with dual chamber pacing. *Pacing Clin Electrophysiol* 1998;21:1175-9.
  16. Stierle U, Krüger D, Vincent AM, et al. An optimized AV delay algorithm for patients with intermittent atrioventricular conduction. *Pacing Clin Electrophysiol* 1998;21:1035-43.
  17. Mayumi H, Kohno H, Yasui H, Kawachi Y, Tokunaga K. Use of automatic mode change between DDD and AAI to facilitate native atrioventricular conduction in patients with sick sinus syndrome or transient atrioventricular block. *Pacing Clin Electrophysiol* 1996;19: 1740-7.
  18. Andersen HR. Optimal pacing in sick sinus syndrome. In: Rosenqvist M, editor. *Cardiac Pacing: New Advances*. London: W.B. Saunders Company Ltd., 1997:83-100.